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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
06/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,135	WEILL ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8, 10, 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 10, 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114, received 03/18/09.

Status of the Claims

Claims 8, 10, and 11 are pending in this application and are the subject of the Office action.

Response to applicant's arguments

Rejection under 112, 2nd paragraph

This rejection is withdrawn in view of the amendment.

Rejection under 102(b)

This rejection is withdrawn in view of the claim amendment canceling the rejected claims.

REJECTIONS

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for methods for increasing the cytotstatic or cytotoxic effects on colon and liver tumor cells, and decreasing the cytotoxic effect on normal leukocytes of cisplatin, oxaliplatin, 5-FU, and taxol, does not reasonably provide

enablement for other tumors, other platinum derivatives, and other anticancer medicinal products. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention

The invention in general relates to a method for increasing the cytostatic or cytotoxic effects on tumor cells, and decreasing the cytotoxic effect on normal leukocytes of an anticancer medicinal product /composition comprising a platinum derivative mangafodipir, wherein said method comprises administering to a patient treated with said anticancer medicinal medical product, an antitumoral and leukocyte-protecting amount of mangafodipir.

Relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical and medical arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmacologic, pharmaceutical, and clinical efficacy. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

State and predictability of the art

Slater (Slater S. Non-curative chemotherapy for cancer- is it worth it? Clinical Medicine. 2001;1(No. 2): 220-222) teaches that most patients with cancer achieve only modest prolongation of survival and limited improvements in the quality of life (page 220, first para.). Slater teaches that drug resistance and the non-selectivity of current conventional therapies limit their use. Slater postulates that with increased funding, and increased awareness of the potential benefits of treatment, could result in real optimism in cancer care (page 222, last para.). Based on the state of the oncology art, there is reasonable doubt that artisan skilled in the art would be able to reasonably and predictability practice the instant claimed invention commensurate with the scope of the claims.

Fino et al. (US Patent 6,828,448) teach platinum derivative compounds (i.e. platinum oxide) as a catalyst (col. 3, lines 23-27). Instant claim 8 also recites the term "platinum derivative." Based on the state of the art, there is reasonable doubt that one would be able to reliably and predictably determine which platinum derivatives may be employed in the practice of the instant claimed invention without conducting extensive experimentation.

The breadth of the claims

The instant claims are relatively broad in scope. For example, claim 8 encompasses any and all patients treated with an anticancer medicinal product. Since cancer represents a group of diverse clinical conditions and are often treated with different therapeutic modalities, one would not reasonably expect that the combination

of mangafodipir and any anticancer medicinal product would reliably or predictable by effective in exhibiting antitumoral and leukocyte-protection in all patients treated with cancer. For example, patients with postmenopausal breast cancer are often treated with hormonal therapy, while patients with acute myelogenous leukemia are often treated with non-hormonal anticancer drugs. Hence, there is reasonable doubt that the instant claimed mangafodipir and anticancer combination therapies would exhibit antitumoral and leukocyte-protecting effects in all cancer patients. As discussed above in connection with Fino et al., the term "platinum derivatives" encompasses anticancer and non-anticancer compounds such that one would not be able to reasonably practice the instant claims commensurate with the scope of the claims without conducting further experimentation to determine the anti-tumor activity species of the platinum derivative compounds encompassed by said term.

The amount of direction or guidance provided and the presence or absence of working examples

The specification discloses specific anticancer medicinal products, including platinum compounds (= cisplatin and carboplatin), anthracycline anticancer drugs, taxane anticancer drugs and in vitro methods showing that the combination of mangafodipir and an anticancer medicinal product (specification, Example 3) and in vivo studies limited to colon and liver cancer (specification, page). However, as discussed above, cancer represent a diverse group of conditions such that one would have to e able to reliably or predictably extrapolate applicant's study results derived from colon and liver cancers to all other cancers without conducting extensive.

The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, claims 8, 10-11 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 8, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses platinum compounds (cisplatin and oxaliplatin) which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 8, 10, and 11 are directed to encompass "platinum derivative" compounds which only correspond in some undefined way to specifically instantly disclosed platinum derivatives (specification, pages 3 and 11). None of the undisclosed compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are

highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined platinum derivative chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not

representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.).

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Federle et al. (Federle et al. Efficacy and safety of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: Results of the U.S. Multicenter phase III clinical trials. Efficacy of early imaging. Journal of Magnetic Resonance Imaging. 2000; 12:689-701), in view of Towart et al. (WO 97/49390) and Vaage et al. (Vaage et al. Therapy of a xenografted human colonic carcinoma using cisplatin or doxorubicin encapsulated in long-circulating pegylated stealth liposomes. International Journal of Cancer. 1999;80(1):134-137; abstract only), as evidenced by Teslascan. www.epgonline.org/viewdrug.cfm/letter/T/ language/LG0001/drugId/ DR004013/ drugName/TESLASCAN.

Federle et al. teach that focal liver disease comprises discrete, space-occupying lesions of the liver and includes abscesses, cysts, and neoplasms (= tumor cells; page 689, lines 1-3). Federle et al. teach that the therapeutic options available for managing focal liver disease includes surgery, cryotherapy, chemotherapy, or radiation). Federle et al. teach mangafodipir trisodium of 5 µmol/kg was shown to enhance liver in normal healthy volunteers, which is 20-fold less than the 0.1 mmol/kg doses generally employed for gadolinium-based contrast agents (page 690, third full para.). Federle disclose results showing enhancement of the liver following injection of mangafodipir in metastatic colon carcinomas (= tumor cells), which means that said patients had existing tumors cells present prior to the administration of mangafodipir (page 695, col. 1, second full para., lines 11-15). Federle et al. disclose that even though mangafodipir trisodium predominantly enhances normal liver tissue, it is distributed proportionally to

vascular perfusion, and other tissues e.g. metastatic tumors (page 699, col. 1, last para.).

However, Federle et al. do not teach mangadofipir in combination with an anticancer medicinal product as claimed by applicant or the instant claimed amount of mangadofipir recited in claim 10.

Towart et al. (WO 97/49390) teach that certain chelating agents, such as Mn(DPDP) and their chelates, are particularly effective in reducing the toxicity of antitumor agent, in particular anthracyclines and paclitaxel (= taxane; page 2, last para. to page 3, first para). Towart et al. exemplify a method of treating male mice comprising intravenously injecting with saline or 10 µmol/kg of MnDPDP (page 19, Example 3).

Vaage et al. (Vaage et al. Therapy of a xenografted human colonic carcinoma using cisplatin or doxorubicin encapsulated in long-circulating pegylated stealth liposomes. International Journal of Cancer. 1999;80(1):134-137; abstract only) disclose that low doses of cisplatin and doxorubicin hydrochloride encapsulated in long-circulating liposomes was found to inhibit the growth of and affect cures of a human colonic carcinoma growing in nude mice (abstract). Vaage et al. state that the liposome-encapsulated cisplatin had minor systemic toxic side effects indicated by an average 9% weight loss; toxicity was not observed with liposome-encapsulated doxorubicin.

It would have be obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited by combining mangafodipir as taught by Federle et al. with any suitable platinum derivative (e.g. cisplatin) as taught by Vaage et al. treat a patient with cancer involving the colon in order to reduce the toxicity

associated with cisplatin. One would have been motivated to do so because Towart et al. suggest that mangafodipir may be effective in reducing the toxicity associated with chemotherapy drugs and both Vaage et al. and Federle et al. are directed to methods of treating patients with cancer involving the colon such that one would reasonably expect that the combination of mangafodipir and cisplatin encompassed by the prior art would result in a reduction in cisplatin-induced toxicity (see In re Kerkhoven, 205 USPQ 1069 (CCPPA 1980). The motivation for combining the components flows from their individually known common utility.

Teslascan is added as evidentiary reference only to show that the teaching of Towart et al. of 10 µmol/kg of MnDPDP (page 19, Example 3) is equivalent to 10 µmol/kg = 6.91 mg/kg mangafodipir.

It is noted that Teslascan (MnDPDP) is considered to be the same as mangafodipir trisodium as taught by Federle et al. as evidenced by the title of the Federle et al. reference.

Regarding claim 8, the prior art encompasses a method of treating a patient with a patient with colon cancer comprising mangafodipir and cisplatin (= platinum derivative) and the instant claims also require mangafodipir and a platinum derivative (= cisplatin). Since the prior art teaches the same instantly claimed combination (mangafodipir and a platinum derivative) to treat the same population (patient with cancer of the colon), one would reasonably expect the method of treatment encompassed by the prior art would also exhibit the same therapeutic effects as claimed.

With respect to the term "an antitumoral and leukocyte-protecting amount of mangafodipir," Towart et al. exemplify a method of treating male mice comprising intravenously injecting with saline or 10 µmol/kg of MnDPDP (page 19, Example 3), which is equivalent to mangafodipir trisodium 6.91 mg/kg mangafodipir, as evidenced by the teaching of Teslascan, overlaps with the instant disclosed dose of mangafodipir recited in instant claim 10. Hence, one would reasonably expect that the amount of mangafodipir as taught by the prior art would also be an antitumoral and leukocyte-protecting amount as claimed.

With respect to the preamble, the prior art encompasses the same instantly claimed combination (mangafodipir + a platinum derivative) to treat the same population (colon cancer), wherein the mangafodipir is present in an amount that overlaps with the instant disclosed amount of mangafodipir, and therefore would also expect that the method encompassed by the prior art would have the same effects as claimed, including increasing the cytostatic or cytotoxic effects on tumor cells, and decreasing the cytotoxic effect on normal leucocytes of an anticancer medicinal product (e.g. cisplatin).

Regarding claim 10, Towart et al. exemplify a method of treating male mice comprising intravenously injecting 10 µmol/kg of MnDPDP (page 19, Example 3), which is equivalent to mangafodipir trisodium 6.91 mg/kg mangafodipir. Hence, the teaching of the prior art overlaps with the instant claimed amount mangafodipir of "from 1 to 100 mg/kg/day."

Regarding claim 11, the above discussion of claim 8 is incorporated by reference.

Thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability

Response to applicant's arguments

In response to applicant's argument that the prior art does not teach or suggest the instant claimed invention, it is noted the prior art encompasses each claimed limitation. Further, applicant's experimental results showing that mangafodipir reduces the toxicity of certain chemotherapy drugs (e.g. platinum derivatives) is not unexpected in view of the teaching of Towart et al. (WO 97/49390) that certain chelating agents, such as Mn(DPDP) and their chelates, are particularly effective in reducing the toxicity of antitumor agents (page 2, last para. to page 3, first para) and cisplatin as encompassed by the prior art is an antitumor agent. Hence, as discussed above, administration of the same drug combination to the same population, wherein the dose of mangafodipir overlaps with the instant claimed amount, would reasonably be expected to exhibit the same therapeutic effects as claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

18 May 2009

/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611